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# A Bayesian Approach to Bergman's Minimal Model

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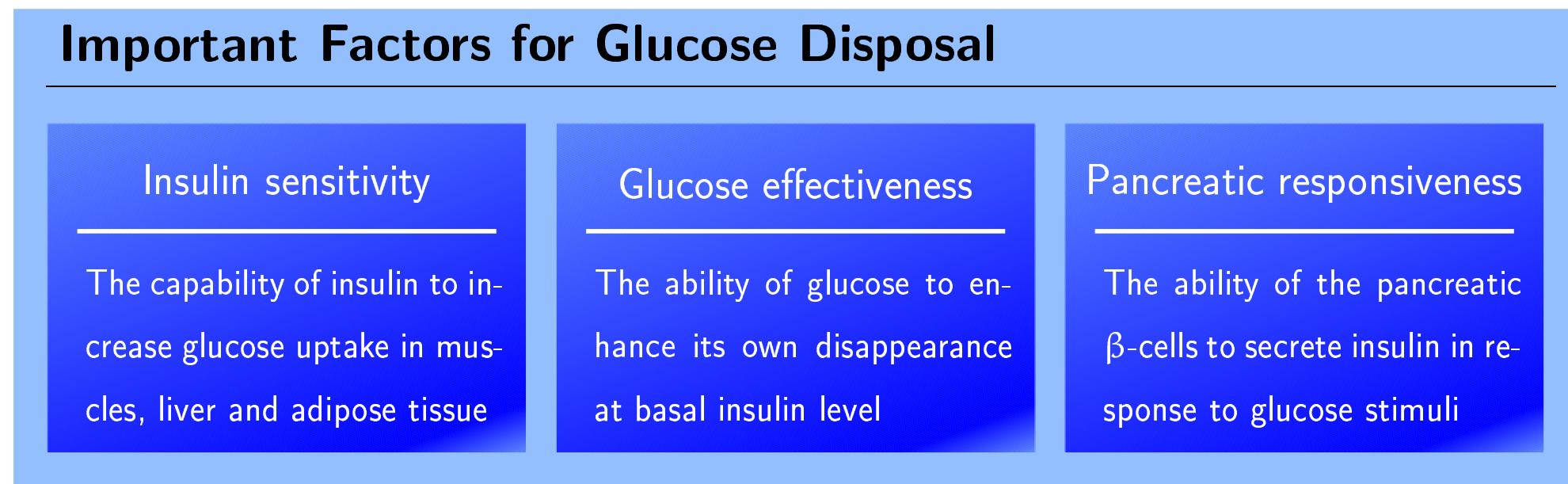
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## Motivation

Diabetes is associated with a number of abnormalities of insulin metabolism ranging from an absolute deficiency of the hormone to a combination of insulin deficiency and resistance causing an inability to metabolise glucose from the blood at normal rates.

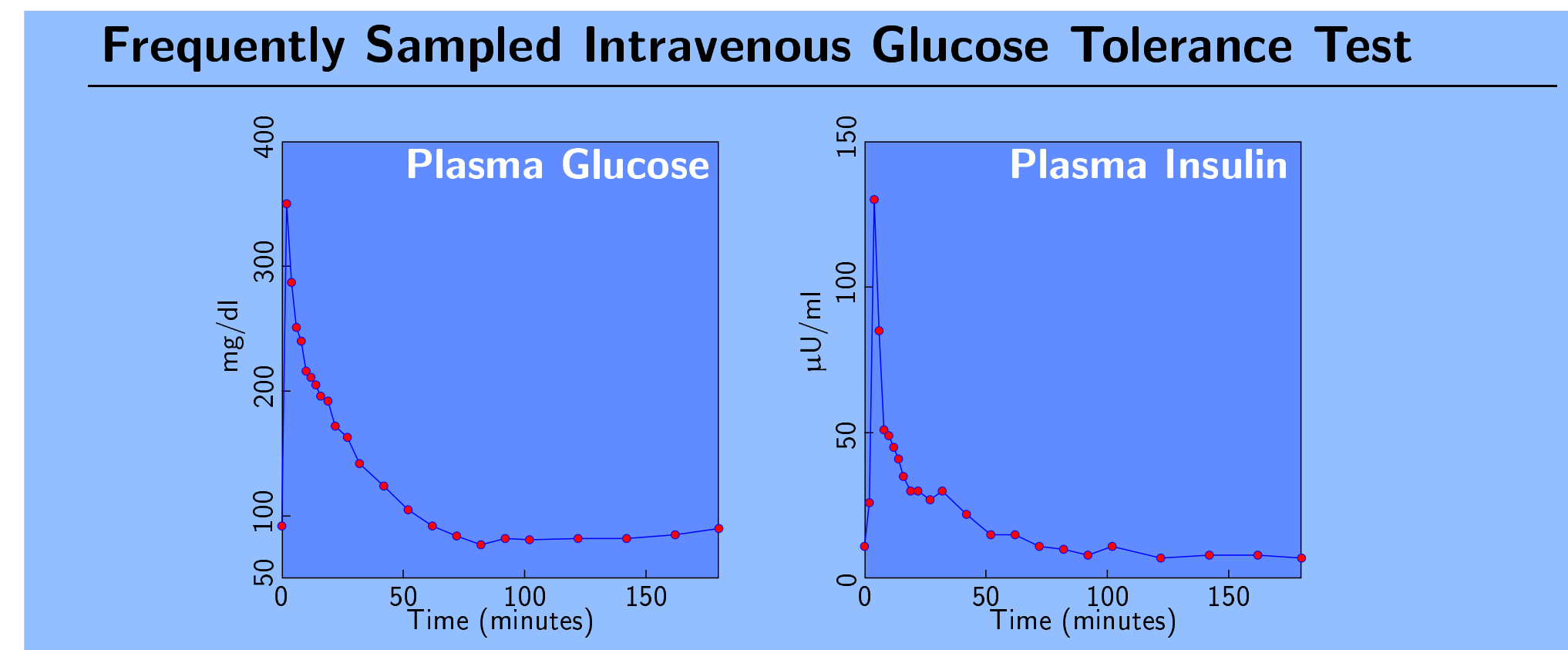
Three factors are recognised to play an important role for glucose disposal.



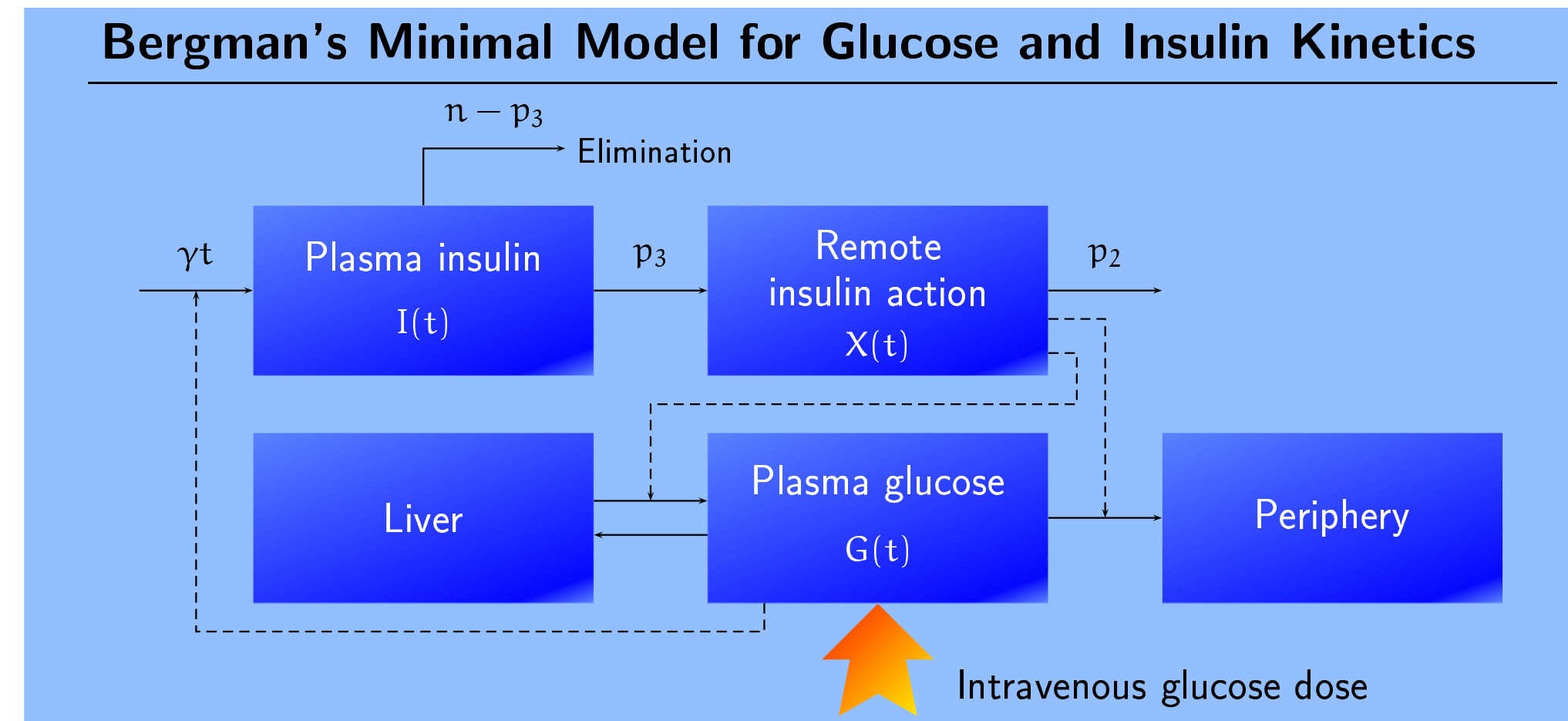
Failure of any of these factors may lead to impaired glucose tolerance, or, if severe, to overt diabetes and assessment of them may improve classification, prognosis and therapy of the disease.

## Bergman's Minimal Model

Quantitative assessment of the factors were made possible by the 'minimal model' (Bergman et al., 1979). The 'minimal model' is based upon an analysis of frequently sampled intravenous glucose tolerance (FSIVGTT) data, where a dose of glucose (usually 0.3 g. of glucose per kg. body weight) is administered intravenously over a 60 seconds period to overnight-fasted subjects. Data from a single experiment is shown below.



The minimal model is based upon a compartmental analysis of the glycaemic system.



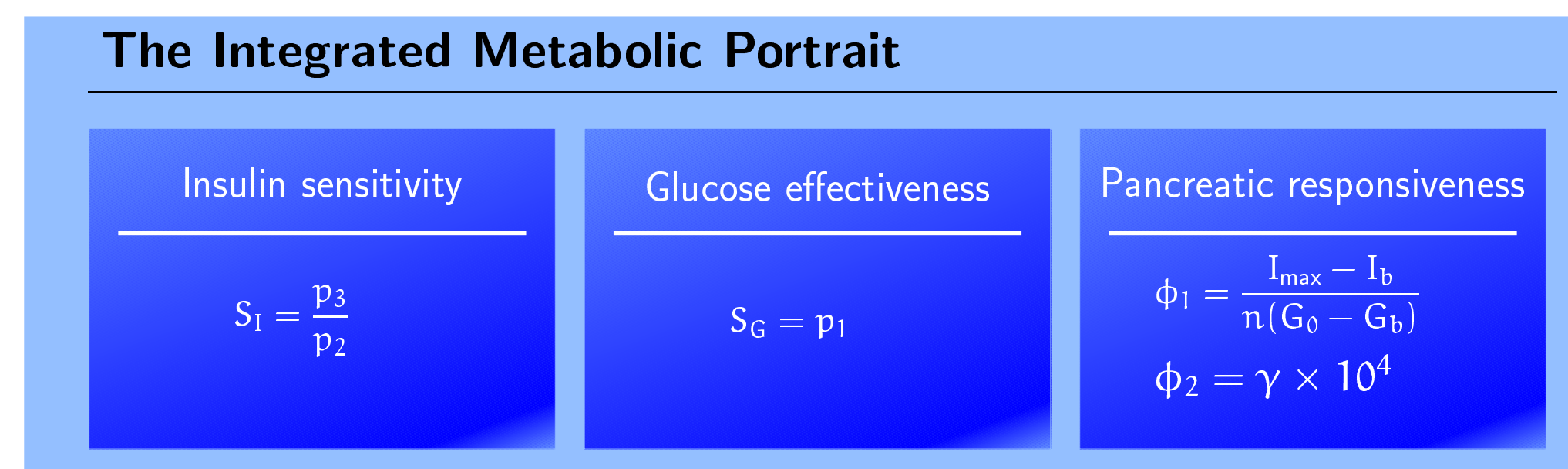
The feedback effect illustrated above may be decomposed into two independent components:

- The effect of glucose to enhance insulin secretion
- The effect of insulin to accelerate glucose uptake,

which by careful compartmental analysis leads to

$$\begin{aligned}
 \dot{I} &= -nI + \gamma(G - h)^+t, & I(0) &= I_0, \\
 \dot{G} &= -p_1(G - G_b) - XG, & G(0) &= G_0, \\
 \dot{X} &= -p_2X + p_3(I - I_b), & X(0) &= 0.
 \end{aligned}
 \tag{1}$$

The metabolic portrait of a single individual is determined by the four parameters:



## What can be done?

### Current Approach

- does not simultaneously take **all three differential equations** into account
- does not consider the **ill-posedness** of the estimation problem
  - ❖ very dependent on good **initial parameter estimates**

but are reasonably **fast**, though not reliable.

### Our Approach

- takes **all three differential equations** into account
- adequately models the **a priori** information
  - ❖ efficient regularisation of the estimation problem
- provides a solution given in terms of **probability distributions**
  - ❖ allows for statistical inference

## Statistical Model

Assume that physiologic variation and discretisation error can be modelled by random white noise processes;  $\epsilon_t^G$ ,  $\epsilon_t^X$  and  $\epsilon_t^I$ . Then by discretisation the non-linear coupled differential equations in (1) become

$$G_{t+1} = [(1 - \Delta t p_1 - \Delta t X_t)G_t + \Delta t p_1 G_b] + \epsilon_t^G \implies G_{t+1} | \mu_{t+1}^G, \tau_G \sim \mathcal{N}(\mu_{t+1}^G, \tau_G^{-1}),$$

$$X_{t+1} = [(1 - \Delta t p_2)X_t + \Delta t p_3(I_t - I_b)] + \epsilon_t^X \implies X_{t+1} | \mu_{t+1}^X, \tau_X \sim \mathcal{N}(\mu_{t+1}^X, \tau_X^{-1}),$$

$$I_{t+1} = [(1 - \Delta t n)I_t + \gamma(G_t - h)^+ \Delta t] + \epsilon_t^I \implies I_{t+1} | \mu_{t+1}^I, \tau_I \sim \mathcal{N}(\mu_{t+1}^I, \tau_I^{-1}).$$

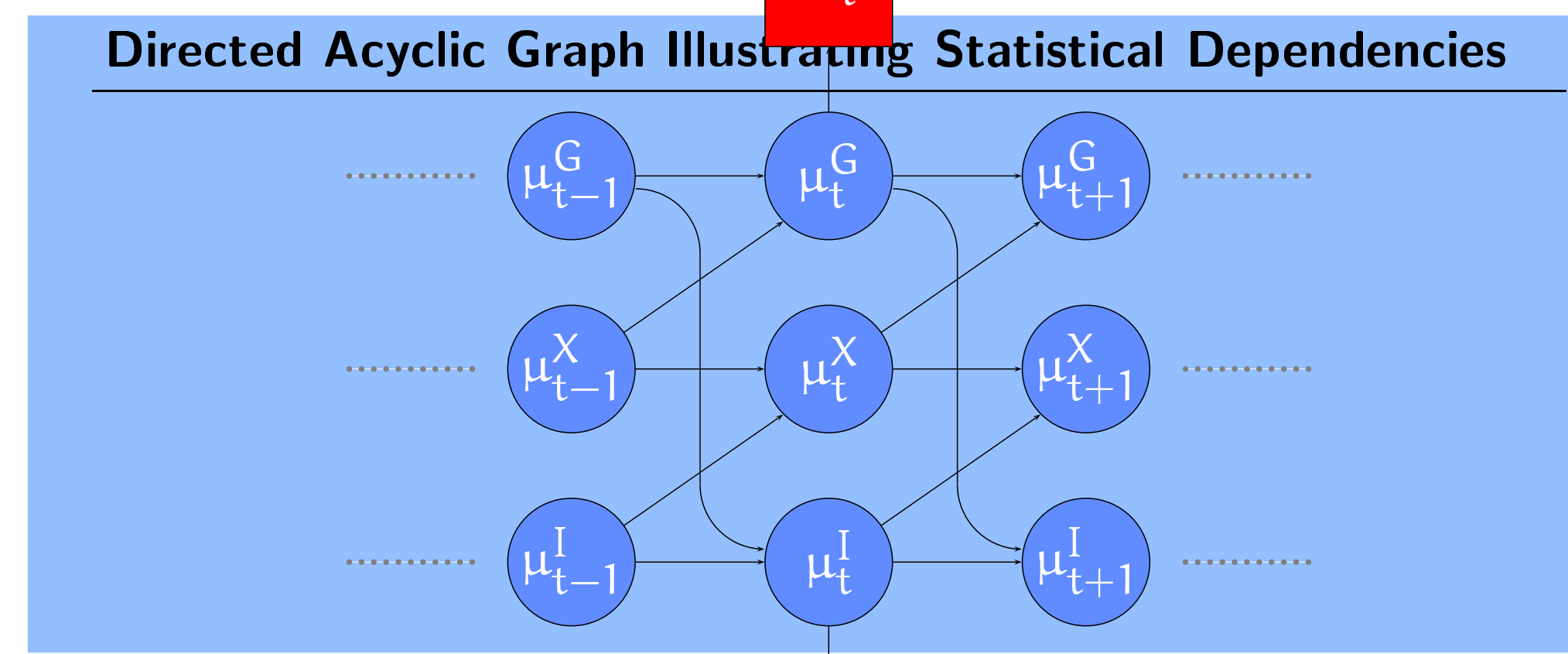
## Statistical Dependencies

### Graphical Model

Directed graphical models (Lauritzen, 1996) represent conditional independence structures of a statistical model through an appropriate factorisation of the density w.r.t. a graph. The vertices  $V$  represent the components of the model and missing links represent conditional independence assumptions. More precisely, the density of  $V$  admits the *recursive factorisation* given as

$$p(V) = \prod_{v \in V} p(v | \text{pa}(v)),$$

where  $p(v | \text{pa}(v))$  is the density of  $v$  given  $\text{pa}(v) = (v)_{v \in \text{pa}(v)}$  and  $\text{pa}(v)$  denotes the parent vertices of  $v$ . The model obtained by discretisation can be illustrated by the following directed acyclic graph



## Simulation Based Inference

Let  $\Theta = (p_1, p_2, \dots, G_{unobs}, X_{unobs}, I_{unobs})$  denote all **unobserved** vertices, where

$$G_{unobs} = \{\text{all unobserved } G_t\text{'s}\} = G \setminus G_{obs}$$

$$X_{unobs} = \{\text{all } X_t\text{'s}\}$$

$$I_{unobs} = \{\text{all unobserved } I_t\text{'s}\} = I \setminus I_{obs}$$

then inference about  $\Theta$  is made by exploring the posterior distribution

$$p(\Theta | \Phi) \propto p(\Theta) L(\Phi | \Theta),$$

where the **observed** data  $\Phi = (G_{obs}, I_{obs})$  enters trough the *likelihood function*  $L(\Phi | \Theta)$  and the *a priori* information is modelled by the *prior density*  $p(\Theta)$ .

Samples from the posterior are obtained by Markov chain Monte Carlo techniques (Metropolis et al., 1953) by successively simulating values from the full conditionals

$$p(v | V \setminus v) \propto p(v | \text{pa}(v)) \prod_{w: v \in \text{pa}(w)} p(w | \text{pa}(w)), \quad v \in \Theta.$$

Hereby an irreducible Markov chain  $\{\Theta_0, \Theta_1, \dots\}$  with state space  $\Theta$  and with stationary distribution  $p(\Theta | \Phi)$  is constructed. See Robert and Casella (1999) for an introduction to MCMC techniques.

## Implementation

### The Metropolis–Hastings Algorithm

1. Propose a candidate  $v'$  from the proposal distribution  $q(v, v')$ .
2. Accept with probability

$$\alpha(v, v') = 1 \wedge \frac{p(v' | V \setminus v') q(v', v)}{p(v | V \setminus v) q(v, v')}.$$

Updating e.g.  $X_t$

Note how the density  $p(X_t | \Phi, \Theta \setminus \{X_t\})$  factorises into

$$p(X_t | \Phi, \Theta \setminus \{X_t\}) \propto p(X_t | X_{t-1}, I_{t-1}) p(X_{t+1} | X_t, I_t) p(G_{t+1} | G_t, X_t).$$

The required conditional densities are

$$\begin{aligned}
 X_t | X_{t-1}, I_{t-1}, \tau_X &\sim \mathcal{N}((1 - \Delta t p_2)X_{t-1} + \Delta t p_3(I_{t-1} - I_b), \tau_X^{-1}) \\
 G_t^I | G_{t-1}, X_{t-1}, \tau_G &\sim \mathcal{N}((1 - \Delta t p_1 - \Delta t X_{t-1})G_{t-1} + \Delta t p_1 G_b, \tau_G^{-1})
 \end{aligned}$$

Now, propose a new candidate  $X_t'$  from a symmetric proposal distribution

$$X_t' | X_t, \sigma^2 \sim \mathcal{N}(X_t, \sigma^2),$$

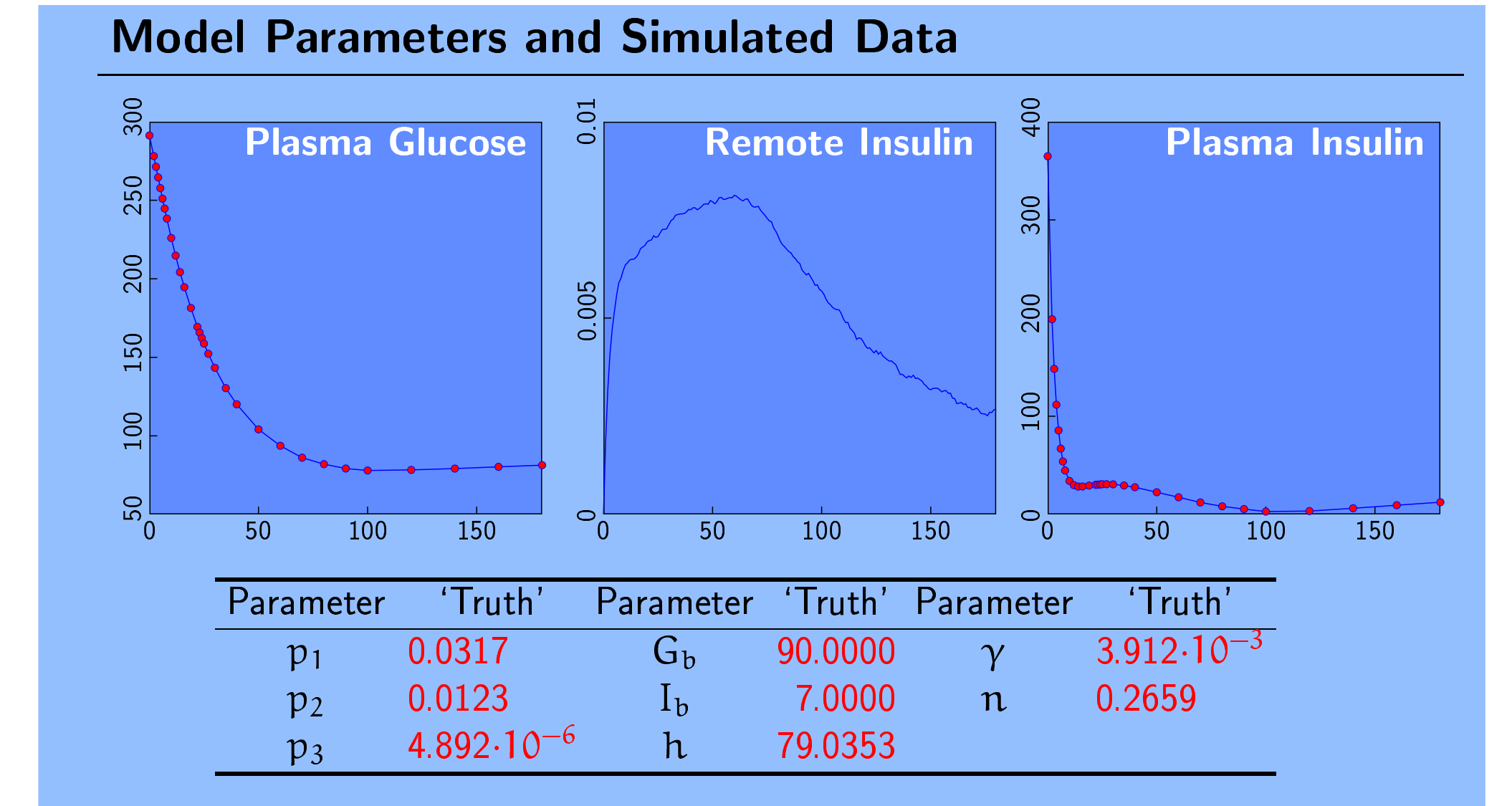
then the acceptance probability  $\alpha$  becomes

$$\alpha(X_t, X_t') = 1 \wedge \frac{p(X_t' | X_{t-1}, I_{t-1}) p(X_{t+1} | X_t', I_t) p(G_{t+1} | G_t, X_t')}{p(X_t | X_{t-1}, I_{t-1}) p(X_{t+1} | X_t, I_t) p(G_{t+1} | G_t, X_t)}.$$

## Simulated Data Example

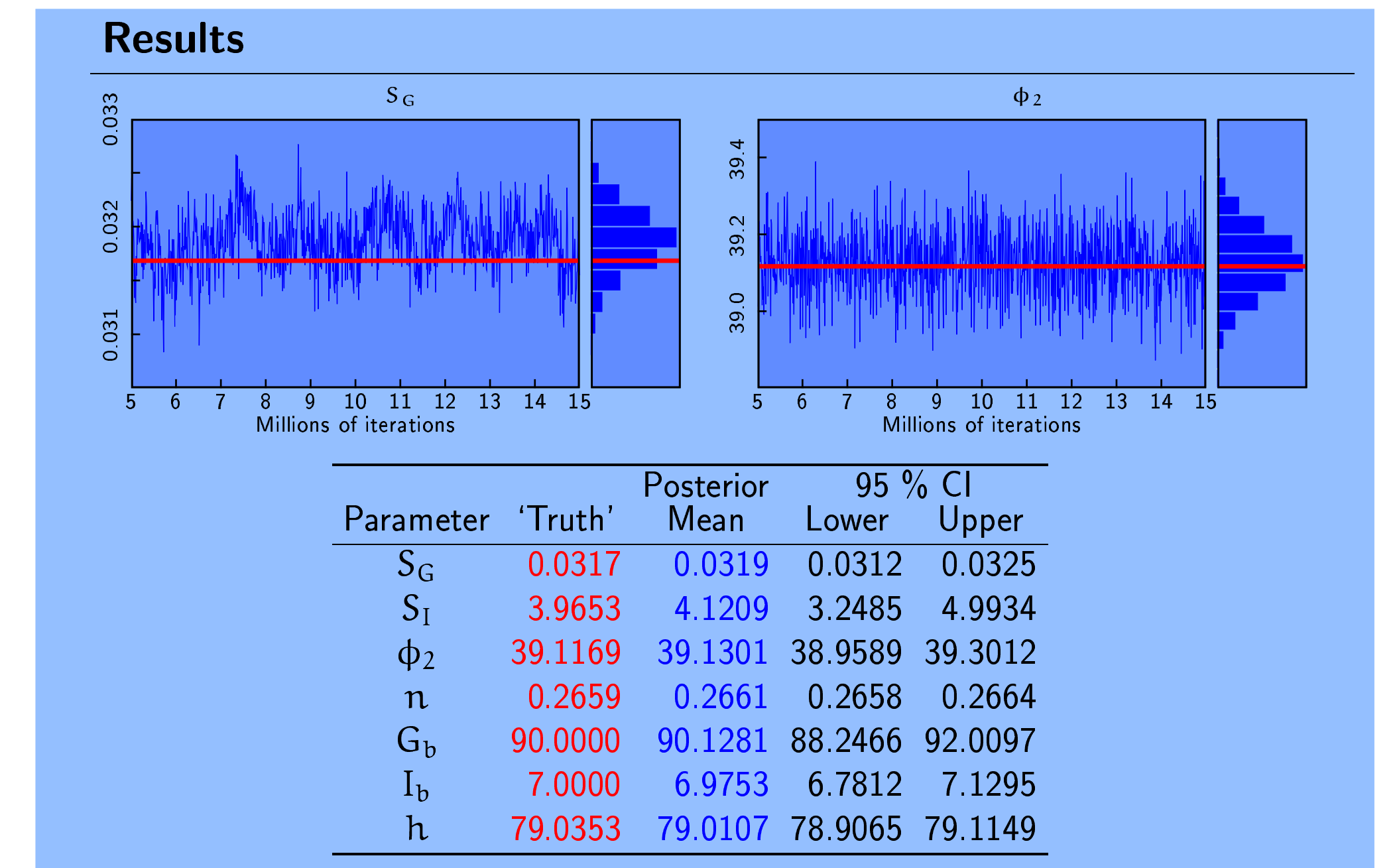
### Simulating Data

In order to investigate the performance of our Bayesian approach to Bergman's minimal model we simulated experimental data from a normal glucose tolerant person. The model parameters and data obtained are given below

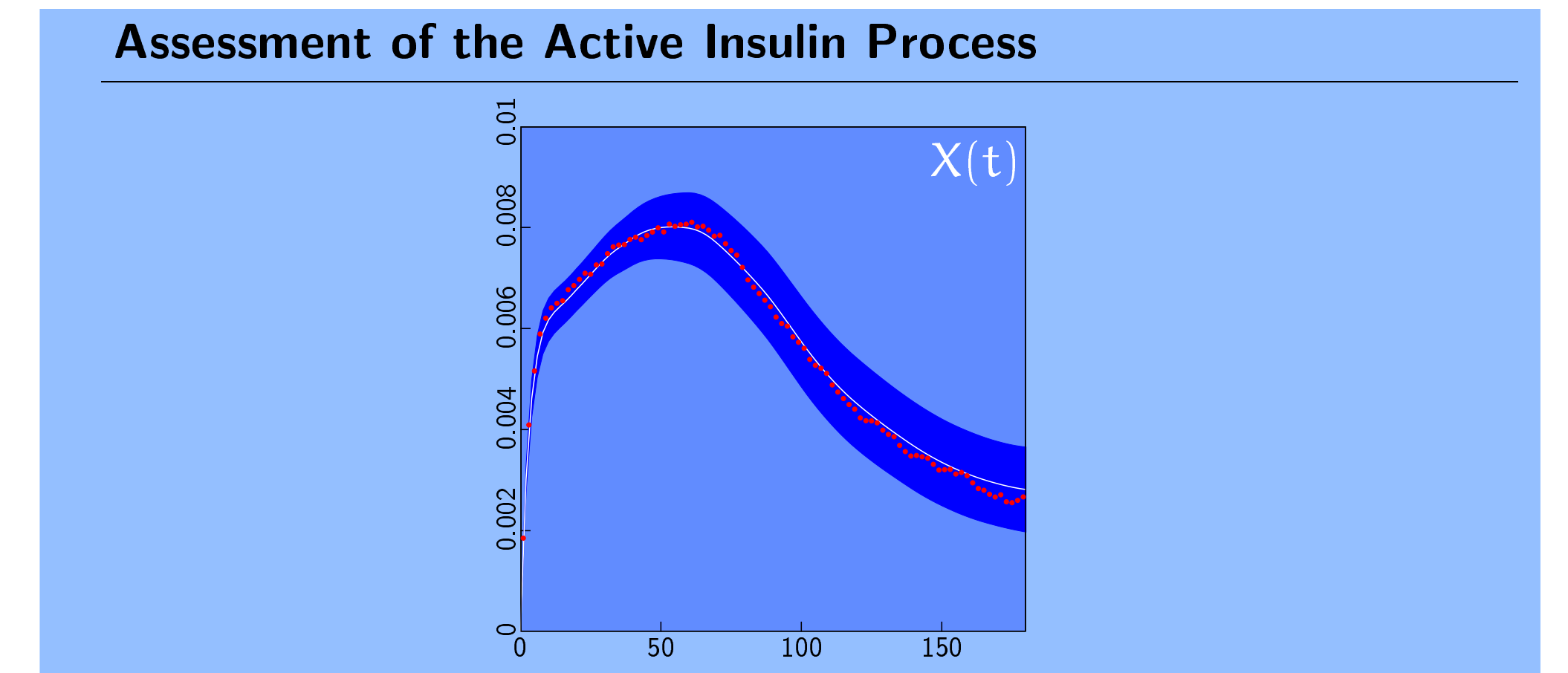


### Results

The Markov chain were run for 15 million iterations. Below is shown summary statistics for the latter 10 million iterations.



Moreover, the active insulin process may be efficiently assessed.



## Discussion

### What has been done ?

We have developed a Bayesian method

- to regularise an ill-posed estimation problem and
- assess the metabolic properties of a single individual from all three differential equations simultaneously

### What needs to be done ?

- Better mixing
  - ❖ Better proposals
  - ❖ Simulated tempering
  - ❖ MCMCMC-techniques

### Future work

- Real data
- Not only allow for physiological variation/discretisation error, but also take measurement error into account
- Extend approach to the **oral glucose tolerance test procedure**
- Extensions to normal populations  $\implies$  inference on e.g. normal metabolic properties.
- Prior sensitivity analysis

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